Low Ultraviolet B and Increased Risk of Brain Cancer: An Ecological Study of 175 Countries

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ABSTRACT

Background. The purpose of this study was to determine whether an inverse association exists between latitude, solar ultraviolet B (UVB) irradiance, modeled 25-hydroxyvitamin D [25(OH)D] levels, and incidence rates of cancer of the brain.

Methods. Associations of latitude and UVB irradiance with age-standardized incidence rates of cancer of the brain were analyzed for 175 countries while controlling for proportion of population overweight, energy from animal sources, fish consumption, cigarette and alcohol consumption, and per capita health expenditures, using multiple regression. Serum 25(OH)D levels were modeled for each country, and their association with brain cancer was also determined.

Results. Incidence rates of brain cancer were higher at higher latitudes (R^2 for males = 0.45, $p < 0.0001$; females $R^2 = 0.35$, $p < 0.0001$). After adjustment for potential confounders, UVB irradiance ($p < 0.0001$) and modeled serum 25(OH)D were inversely associated with incidence rates.

Conclusions. Countries with low solar UVB irradiance and estimated mean serum 25(OH)D levels generally had higher age-standardized incidence rates of brain cancer. Since this was an ecological study, further research would be worthwhile of the association of prediagnostic serum 25(OH)D with incidence rate in studies of cohorts of individuals.

INTRODUCTION

Worldwide there are an estimated 189,485 cases and 141,650 deaths from primary brain cancer each year (1). In the United States, 21,810 cases and 13,070 deaths were expected in 2008 (2). However, very little is known about the etiology of primary brain cancer with the principal confirmed causes being ionizing radiation and a few uncommon genetic syndromes (3).

Greater exposure to solar ultraviolet B (UVB) in areas with high solar irradiance results in greater cutaneous photosynthesis of vitamin D in populations in these areas, resulting in higher levels of vitamin D metabolites, particularly 25-hydroxyvitamin D (25[OH]D) that are associated with lower incidence rates of certain cancers (4). Populations living at higher latitudes, or having lower prediagnostic serum 25(OH)D levels, have higher incidence rates of cancers of the breast (5-8), colon (9-12), and ovary (13), raising the possibility that vitamin D might also play a similar beneficial role in the etiology of cancer of other sites, such as the brain.

Tumors of the brain and nervous system are markedly different from tumors originating in other sites. However, it is possible that vitamin D may play a role in prevention of brain cancer through its ability to help maintain the structural integrity of intercellular adhesion proteins. These adhesion proteins can be degraded by ionizing radiation, the principal known risk factor for brain cancer. In addition, vitamin D_3 (cholecalciferol) has been shown to induce death of human glioblastoma cells in vitro (14) and another study

found that 25(OH)D can cause a significant reduction in growth of glioblastoma cells in vitro (15).

We chose several variables to include in the model as possible confounders based on previous research. It is well known that obesity is associated with lower levels of circulating serum 25(OH)D (16) as well increased risk for several cancers (17). Intake of large quantities of energy of animal origin is thought to increase a growth hormone, Insulin-like Growth Factor I (IGF-I), which is believed to increase risk of cancer for other sites (18-20)and may possibly be relevant to the etiology of brain cancers.

Consumption of fish and fish oil are good sources of dietary vitamin D, they also exert a beneficial effect on age-related cognitive decline (21). Cigarette smoking is a well established risk factor for many cancers and some evidence exists that implicates parental drinking in increasing risk of childhood brain cancer (22, 23) raising the possibility that alcohol use may play some role in the etiology of certain brain cancers. Per capita health expenditure was included in the analysis in order to account for international differences in quality of health care and the ability to detect cancers, which may be correlated with latitude since countries at higher latitude tend to be wealthier than countries at lower latitudes.

Multiple linear regression was used to examine the associations of UVB irradiance adjusted for cloudiness with age-standardized incidence rates of cancer of the brain, while controlling for potential confounders such as proportion of the population

overweight, intake of energy from animal sources, fish consumption, cigarette and alcohol consumption, and per capita health expenditures.

MATERIALS AND METHODS

Data Sources

Age-standardized incidence rates of brain cancer were obtained for 175 countries, along with latitude of the population centroid of each country, winter UVB irradiance adjusted for cloudiness, proportion of the population overweight, intake of energy from animal sources, intake of energy from fish sources, per capita alcohol and cigarette consumption and per capita health expenditures. All 175 countries were used in the latitude analysis. Complete data on all other variables were available for 107 countries, and were used in the multivariate analyses.

The sources for many of the variables have been described elsewhere (24). Age-standardized incidence rates of brain and nervous center tumors (defined as ICD 10 codes C70-C72) were obtained using the International Agency for Research on Cancer (IARC) GLOBOCAN database for 2002, the latest year for which data are available (1). Per capita consumption of cigarettes, alcohol, and energy from animal and fish sources were obtained from the United Nations (UN) Food and Agriculture Organization for 1980 (25). Data on cloud cover were obtained from the National Aeronautics and Space

Administration International Satellite Cloud Climatology Project (ISCPP) earth-orbiting satellite (26).

Serum 25(OH)D values were modeled for 157 countries for which actual measurements of 25(OH)D from population based samples were not available. We were able to obtain actual serum 25(OH)D measurements from 28 regions in 18 countries from previous research, and these actual measurements provided the basis for modeling estimated population 25(OH)D values. Estimated serum 25(OH)D was modeled using the measured levels of serum 25(OH)D during winter obtained from 28 regions in 18 countries (Appendix Table 1) as the dependent variable, UVB irradiance as the independent variable and skin pigmentation levels in the areas where the studies were performed as a covariate. A multiple regression model based on known values of these variables, provided regression coefficients for use in a separate multiple regression prediction equation that was used to estimate mean winter serum 25(OH)D levels in countries where measurements were not available. The prediction equation included a scaling constant that was empirically determined. The measured 25(OH)D levels were used in the final calculations for the 18 countries, and the values modeled from the procedures described above were used for the remaining 157 countries.

Statistical analysis

Age-standardized incidence rates from GLOBOCAN (1) were analyzed according to the latitude of the population centroid. The rates were age-standardized to the age

distribution of the 2000 world population (1). The best fit to the data points was obtained using a polynomial trend line. A standard pharmacologic dose-response curve was plotted using a standard algorithm (Prism)(San Diego: GraphPad Software). Multiple linear regression was employed to examine the associations of UVB irradiance adjusted for cloudiness, while controlling for proportion of the population overweight, intake of energy from animal sources, fish consumption, cigarette and alcohol consumption, and per capita health expenditure in 107 countries. All analyses were performed using SAS Version 9.1 and JMP Version 5.1.2 (Cary NC: SAS Institute).

RESULTS

Incidence rates of brain cancer were higher at higher latitudes, with a roughly parabolic relationship (Figures 1-2). According to multivariate analysis in males, UVB irradiance was independently inversely associated with incidence rates ($p < 0.0001$). In addition, the proportion of the population overweight ($p = 0.04$) and intake of energy from animal sources ($p = 0.01$) were positively associated with incidence rates, while intake of energy from fish was inversely associated ($p = 0.02$) (Table 1).

According to a multivariate analysis in females, UVB irradiance ($p < 0.0001$) was independently inversely associated with incidence, similar to the association in males (Table 2). No other covariates were associated with incidence in females. Serum 25(OH)D also was inversely associated with incidence rates, according a dose-response analysis performed for both sexes combined, based on modeled and measured serum levels of 25(OH)D (Figure 3).

DISCUSSION

The etiology of brain cancer is still poorly understood. This is the first report of the inverse association of incidence rates of solar UVB irradiance with cancer of the brain, to our knowledge. Incidence rates of cancer of the brain were higher in countries located at latitudes distant from the equator, where UVB irradiance is low, than in countries closer to the equator, where it is high. In the mulitvariate model, UVB irradiance was inversely associated with brain cancer incidence rates in both sexes even after controlling for other factors. UVB irradiance varies inversely with latitude (27), and photosynthesis in the skin resulting from it is the source of approximately 95% of circulating vitamin D and its metabolites in humans (28). Previous studies have shown that 25(OH)D (14) and its precursor, vitamin D_3 (15), can inhibit growth or destroy human glioblastoma cells in vitro

Several mechanisms are involved in vitamin D anticarcinogenesis (19, 20). A 7-phase sequence has been proposed under the acronym DINOMIT that includes decoupling (D) of epithelial cells due to loss of intercellular adhesion proteins, initiation (I) due to chemical carcinogens, ionizing radiation, infidelity of DNA reproduction, and, possibly, epigenetic factors (19,20). This may be followed by natural selection (N) of rapidly-reproducing clones within a tissue compartment, overgrowth (O) of the tumor mass and penetration of the basement membrane, and, eventually metastasis (M) to remote tissues. It has been hypothesized that with vitamin D adequacy, an involutional (I) or dormant state may occur. If this does not occur, death may ensue. If it does occur, there may be a

transition (T) to permanent dormancy as long as vitamin D adequacy is maintained. (29, 30). Other mechanisms may also be involved, since vitamin D metabolites induce differentiation of cancer cells, including lung cancer cells (31) in tissue culture, and arrest growth by mitotic arrest in the interphase (G0/G1) phase of the mitotic cycle. $1,25(OH)_2D$ enhances apoptosis of epithelial cells in tissue culture by decreasing phospho-Erk (P-Erk) and phospho-Akt (P-Akt), kinases that regulate apoptosis, and pathways up-regulating MEKK-1, a pro-apoptotic signaling molecule (32). Recent studies of the human tumor suppressor oncogene, p53 (33), and its murine analog, p63 (34) have shown that their gene products induce synthesis of vitamin D receptor, a molecule that may mediate the actions of vitamin D on intercellular adhesion.

Vitamin D metabolites are lipid-soluble, and it has been established that 1,25(OH)2-vitamin D readily crosses the blood-brain barrier (35). About 2,400 micrograms of 1,25(OH)2D are present in the parenchyma of the human brain (35). The normal range of serum 1,25(OH)2-vitamin D is 18-64 micrograms/ml (36).

Cancers of the brain have diverse pathological features, but the majority (approximately 60%, including gliomas and glioblastomas) have histological features that are suggestive of glial cell origin (37). Recent evidence suggests that these tumors arise mainly, or perhaps exclusively, from glial stem cells (38), although it has not been definitely ruled out that some might arise directly from glia (39). Glia are derived during embryogenesis from the ectodermal layer (40). Under normal conditions, the number of glial cells in the human brain is approximately equal to the number of neurons (41). Unlike neurons

within the mature central nervous system, several types of glial cells undergo mitosis (39).

Intercellular tight junctions bind glial cells tightly to one another (42), with the exception of microglia, which are mobile (43). The tight junctions of glial cells and associated myelin sheaths help provide a high-resistance barrier that insulates axons and allows rapid transmission of nerve impulses (44). When tight junctions are weak or absent, the speed of transmission of impulses is reduced (44). Tight junctions are upregulated by vitamin D metabolites in several tissues, including colonocytes (45), keratinocytes (46) and renal cells (47), However it has not been established that tight junctions of glial cells are regulated by vitamin D. However, regulation of tight junctions is an established physiological role of vitamin D metabolites in multiple tissues.. Therefore it is likely that vitamin D upregulates tight junctions between glial cells.

Several factors influence risk of cancer of the brain, including history of some infections (48), exposure to ionizing radiation (49), and genetic predisposition (50). However, a subset of tumors that may be due to vitamin D inadequacy might be explained, in part, by a multi-phase process that may begin with loss of intercellular adherence and contact inhibition of glial cell proliferation (4), potentially resulting from vitamin D inadequacy. Weakening of tight junctions and loss of contact inhibition is the first of several proposed phases in evolution within a tissue compartment to early precursors of cancer (4, 51)

Contact inhibition is a well-established anticancer mechanism that arrests mitosis when cells in a tissue compartment (or tissue culture) reach high density (52). In the absence of contact inhibition, which occurs due to many reasons including vitamin D inadequacy, inappropriate proliferation may occur, and is a first step toward a population of cells that may be regarded as potential cancer precursors (4).

In this analysis, per capita energy from fish consumption was significantly inversely associated with incidence rates in men. It is unclear what role, if any, fish consumption plays in preventing brain cancer, however previous research has identified a beneficial effect of fish consumption on age-related cognitive decline (21). On the other hand, some types of fish and fish oil are sources of vitamin D. Although some evidence exists that implicates parental drinking in increasing risk of childhood brain cancer (22, 23), per capita alcohol consumption was not related to incidence rates of brain cancer in this study.

We also found that consumption of energy from animal sources was significantly associated with higher risk of brain cancers in men but not in women. High intake of energy from animal sources, primarily red meat, may increase risk for several other cancers by raising levels of Insulin-like Growth Factor I (IGF-I) (18-20). However, it is unclear what role IGF-I may play in the etiology of brain cancer and how that relationship may be modified by sex. This should be explored further in future observational studies of individuals. It is also possible that consumption of energy from

animal sources is primarily a marker for socioeconomic status, despite the inclusion of per capita health expenditure in the multivariable model.

Per capita health expenditure was not positively associated with brain cancer incidence rates in either sex. As stated before, this variable was included in the analysis in order to account for international differences in quality of health care and the ability to detect cancers, which may be correlated with latitude since countries at higher latitude tend to be wealthier than countries at lower latitudes. However, it is possible that the effect of per capita health expenditure in this model may have been weakened by the inclusion of intake of energy with animal protein, which is also related to socioeconomic status. Nevertheless, UVB irradiance was significantly inversely associated with brain cancer risk despite the inclusion of these variables.

The high incidence of brain cancer in Macedonia, Croatia and Greece remains unexplained. However, it seems possible that the traditional agrarian practices in those countries, combined with a high ovine population, might account for some of the excess(53, 54). Since rural areas of these countries use traditional methods for raising, maintaining and slaughtering livestock, there is inevitable contact of members of the population with sheep and lambs, in which Toxoplasma gondii infection is very widely endemic in the region.

Schuman and colleagues demonstrated that patients with brain cancer (especially gliomas, the most common type) were substantially more likely to have antibodies in the

serum to Toxoplasma gondii (48). A later study confirmed the association, although it reported that the effect was confined to meningiomas (55). A large observational study found that sheep handlers had an odds ratio of 2.7 (95% confidence interval 1.4-5.3) for brain cancer (56).

Other possibilities may include the presence of health care systems especially well suited to detecting cases of brain cancer, use of industrial pesticides that are banned in US, but may still be used in the Balkans, or employment in regional chemical and refining industries. More research would be worthwhile to determine the reasons for the high incidence rates in these countries, compared to most other countries at similar latitudes.

Strengths

This study had several strengths. No other studies have analyzed incidence rates by latitude and UVB irradiance in a large number of countries located at widely different latitudes, to our knowledge. It accounts for several potential risk factors using multiple linear regression. The regression model accounted for 74% of the variation in age-standardized incidence rates of brain cancer in men and 63% in women. The independent inverse association of UVB irradiance with incidence rates of brain cancer, persisted after controlling for these factors.

The percentage of variation in incidence rates of cancer of the brain among countries that was accounted by the regression model that included UVB irradiance and covariates was

similar to that of cancers for which a role of vitamin D has been reported in observational studies of individuals, including those of the breast (R^2 for the model= 0.55, p<0.0001) (57), colon (R^2=0.68, p<0.0001)(57), and ovary (R^2=0.60, p<0.0001) (58).

Limitations

A major limitation of this study is the lack of distinction between types of brain and nervous system tumors. The two most common types of brain cancer are gliomas and meningiomas. These tumors are vastly different from each other and should avoid being grouped together in the same category whenever possible. However, in the only source from which global incidence rates of brain cancer are publicly available, the IARC GLOBOCAN database, no distinction is made between the different types of brain and nervous system tumors. All diagnoses falling under ICD 10 codes C70-C72 are grouped into the same category. Therefore, it is impossible to tell for which tumor, if any, that UVB and vitamin D status may be possible factors in preventing.

Another limitation was the lack of a comprehensive database with information by country on exposure to ionizing radiation or prevalence of genetic factors that increase risk. Furthermore, this study could not account for differences in culture, behaviors, and diet that vary across countries and latitudes which may modify risk of brain cancer. For example, absorption of UVB irradiance by clothing could not be measured in the present study, yet it is possible that the association of UVB with incidence rates of bladder cancer could have been influenced by the type of clothing worn. Since there was no systematic

source of information available on clothing characteristics according to country, it was not possible to eliminate this possible interaction.

Data for several of the potential confounders were from 1980. This was done in order to allow for the 20-30 year latency period necessary for most cancers to develop post-exposure (59). Nevertheless, it is possible that significant shifts in these and other lifestyle habits that occurred over this time period as a result of economic development and globalization could have had a strong impact on risk of brain cancer. However, there was now way to directly assess this in the current model given the data available to the investigators.

Studies such as the present study should be considered as hypothesis-generating, rather than definitive. This was a study of aggregate populations rather than individual subjects. Findings that apply to aggregates may not always apply equally to individuals (60). For example, all individuals living in areas of high UVB irradiance may not have high exposure to UVB. This can result from urbanization and industrialization. On the other hand, regional solar UVB irradiance tends to affect a broad range of individuals, and the association was present despite the possible misclassification of exposure. While nondifferential classification of exposure is possible in ecological studies, it generally obscures associations, rather than creating them (61).

Ecological studies are potentially the source of variables to be investigated using other methods. Still, the diverse geographic distribution of populations in areas with widely

different levels of solar UVB irradiance provides a natural experiment on a large scale. Natural experiments can be of value in identifying potentially relevant etiological factors. For example, ecological comparisons of areas with high fluoride levels in drinking water with areas with low levels showed that higher fluorine content was associated with lower incidence of dental caries (62).

Despite their value for identifying new ideas for research, ecological studies usually cannot account for all possible confounders such as exposure to ionizing radiation by country, or differences in ability to diagnose cancer of the brain. To our knowledge, no comprehensive database on exposure to ionizing radiation by country exists, and, as a result this could not be included in the analysis. The covariate for per capita health care expenditures may control for international variation diagnostic capabilities to some extent. No covariate was available besides this to control for diagnostic differences. Many of these limitations could be addressed by observational studies of individuals. Such studies should be performed to more definitively examine hypotheses generated from natural experiments such as the present study.

CONCLUSION

Further investigation is warranted to confirm the associations observed in this study with observational studies of individuals. New research on the association of the prediagnostic serum 25-hydroxyvitamin D levels of individuals with their risk of brain cancer might be particularly informative.

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Table 1. Solar ultraviolet B irradiance and other covariates in association with brain cancer incidence rates, 107 countries, males, 2002

Variable	Regression coefficient	Standard error	*t*	*p*
Solar UVB irradiance[*]	-0.2219	0.0541	-4.11	<0.0001
Fish consumption[§]	-0.0082	0.0034	-2.37	0.02
Proportion of population overweight[‡]	0.3681	0.0181	2.03	0.04
Intake of energy from animal sources[§]	0.0019	0.0007	2.61	0.01
Alcohol intake[§]	-0.0019	0.0024	-0.81	0.42
Cigarette consumption[¶]	0.0002	0.0002	1.01	0.32
Per capita health expenditure[†]	0.0004	0.0002	1.47	0.14
Intercept	4.1131	0.7596	5.41	<0.0001

$R^2 = 0.74$, $p < 0.0001$

[*]Watts/m^2 at vernal equinox, adjusted for cloudiness

[†]All currencies were adjusted by W.H.O. to U.S. dollars. Source: World Health Organization.

[‡]Source: World Health Organization

[§]Source: United Nations Food and Agriculture Organization

[¶]Source: World Health Organization

Table 2. Solar irradiance and other covariates in association with brain cancer incidence rates, 107 countries, females, 2002

	Regression	Standard

Variable	coefficient	error	*t*	*p*
Solar UVB irradiance[*]	-0.2143	0.0466	-4.60	<0.0001
Fish consumption[§]	-0.0034	0.0029	-1.16	0.25
Proportion of population overweight[‡]	0.0117	0.0085	1.37	0.17
Intake of energy from animal sources[§]	0.0009	0.0006	1.49	0.14
Alcohol intake[§]	-0.0018	0.0021	-0.88	0.38
Cigarette consumption[¶]	0.0002	0.0002	1.05	0.29
Per capita health expenditure[†]	0.0002	0.0002	0.94	0.35
Intercept	3.8424	0.6615	5.81	<0.0001

$R^2 = 0.63$, $p < 0.0001$

[*]Watts/m^2 at vernal equinox, adjusted for cloudiness

[†]All currencies were adjusted by W.H.O. to U.S. dollars. Source: World Health Organization.

[‡]Source: World Health Organization

[§]Source: United Nations Food and Agriculture Organization

[¶]Source: World Health Organization

Appendix Table 1. Mean population 25(OH)D levels from 28 published studies

Author	Year	Journal	Location	Mean 25(OH)D ng/ml
Mazess et al.	1985	Am J Clin Nutr	Alaska, USA	16.6
Oliveri et al.	1990	Medicina	Buenos Aires, Argentina	19.0
Xue et al.	1991	Zhonghua Yu	Beijing, China	17.7
Chailuikit et al.	1996	J Med Assoc Thai	Thailand	67.4
Chapuy et al.	1997	Osteoporos Int	France	17.9
Aloia al.	1998	J Lab Clin Med	New York, USA	27.5
Harris et al.	1998	Am J Clin Nutr	Boston, USA	25.0
Bettica et al.	1999	Osteoporos Int	Italy	18.7
Guillemant et al.	1999	Osteoporos Int	Paris, France	8.6
Kristal-Boneh et al.	1999	Eur J Epidemiol	Israel	25.4
Goswami et al.	2000	Am J Clin Nutr	New Dehli, India	19.6
Brot et al.	2001	Br J Nutr	Denmark	26.2
Mishal et al.	2001	Osteoporos Int	Amman, Jordan	14.4
Nakamura et al.	2001	Nutrition	Japan	14.1
Vieth et al.	2001	Eur J Clin Nutr	Toronto, Canada	24.1
Looker et al.	2002	Bone	USA	26.2
Nesby-O'Dell et al.	2002	Am J Clin Nutr	USA	32.9
Rucker et al.	2002	Cmaj	Calgary, Canada	23.8
Tangpricha et al.	2002	Am J Med	USA	29.1
Fassi et al.	2003	Medicina	Buenos Aires, Argentina	22.0
Arya et al.	2004	Osteoporos Int	Lucknow, India	12.3

Hashemipour et al.	2004	BMC Public Health	Tehran, Iran	8.6
MacFarlane et al.	2004	J Steroid Biochem Mol Biol	Brussels, Belgium	13.8
Premaor et al.	2004	Endocrine	Porto Algere, Brazil	12.0
Rejnmark et al.	2004	Calcif Tissue Int	Greenland	12.1
Tangpricha et al.	2004	Endocr Pract	USA	28.3
Meddeb et al.	2005	Osteoporos Int	Tunis, Tunisia	22.0
Rockell et al.	2005	J Nutr	Dunedin, New Zealand	22.0

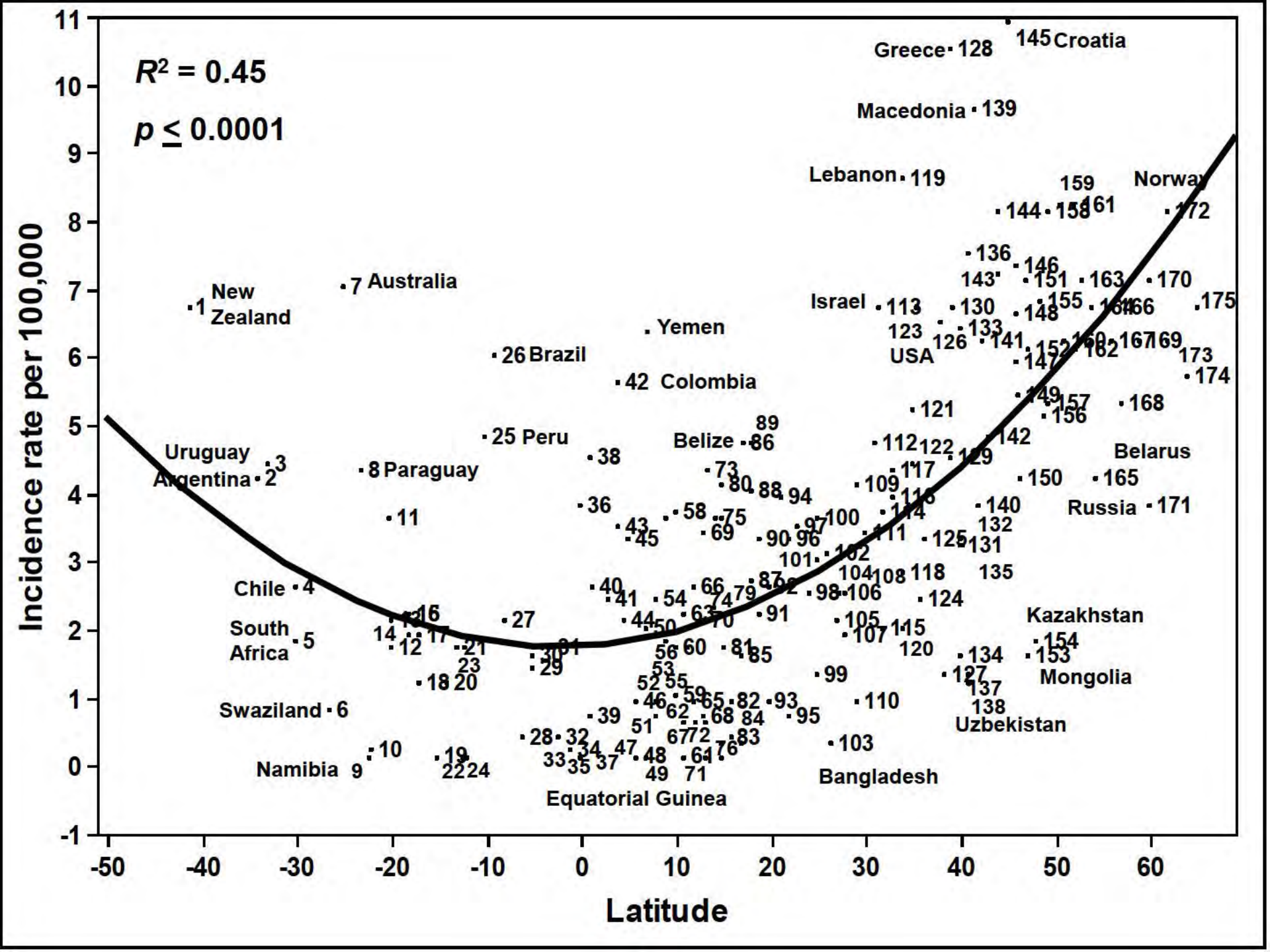
Figure 1. Annual age-standardized incidence rates of cancer of the brain per 100,000 population, males, 175 countries, 2002. Source: Data from GLOBOCAN (1).

1. New Zealand; 2. Argentina; 3. Uruguay; 4. Chile; 5. South African Republic; 6. Swaziland; 7. Australia; 8. Paraguay; 9. Namibia; 10. Botswana; 11. Mauritius; 12. Madagascar; 13. Zimbabwe; 14. Fiji; 15. Mozambique; 16. Vanuatu; 17. Bolivia; 18. Polynesia; 19. Zambia; 20. Samoa; 21. Melanesia; 22. Angola; 23. Comoros; 24. Malawi; 25. Peru; 26. Brazil; 27. Solomon Islands; 28. Tanzania; 29. Indonesia; 30. Papua New Guinea; 31. Burundi; 32. Rwanda; 33. Congo Brazzaville; 34. Gabon; 35. Congo; 36. Ecuador; 37. Equatorial Guinea; 38. Kenya; 39. Uganda; 40. Singapore; 41. Malaysia; 42. Colombia; 43. Suriname; 44. Brunei; 45. Guyana; 46. Benin; 47. Cameroon; 48. Liberia; 49. Central African Republic; 50. Sri Lanka; 51. Cote d'Ivoire; 52. Ghana; 53. Togo; 54. Venezuela; 55. Sierra Leone; 56. Ethiopia; 57. Panama; 58. Costa Rica; 59. Nigeria; 60. Somalia; 61. Guinea; 62. Micronesia; 63. Trinidad and Tobago; 64. Djibouti; 65. Guinea-Bissau; 66. Philippines; 67. Burkina Faso; 68. Cambodia; 69. Nicaragua; 70. Barbados; 71. Gambia; 72. Guam; 73. El Salvador; 74. Senegal; 75. Guatemala; 76. Chad; 77. Honduras; 78. Sudan; 79. Thailand; 80. Yemen; 81. Eritrea; 82. Cape Verde; 83. Niger; 84. Mali; 85. Viet Nam; 86. Belize; 87. Lao People Democratic Republic; 88. Jamaica; 89. Puerto Rico; 90. Dominican Republic; 91. Haiti; 92. India; 93. Mauritania; 94. Cuba; 95. Myanmar; 96. Oman; 97. Mexico; 98. Bahamas; 99. Qatar; 100. Saudi Arabia; 101. United Arab Emirates; 102. Bahrain; 103. Bangladesh; 104. Egypt; 105. Libya; 106. Bhutan; 107. Algeria; 108. Nepal; 109. Kuwait; 110. Lesotho; 111. Pakistan; 112. Jordan; 113. Israel; 114. Iran; 115. Morocco; 116. China; 117. Iraq; 118. Afghanistan; 119. Lebanon; 120. Tunisia; 121. Cyprus; 122. Syria; 123. Malta; 124. Japan; 125. South

Korea; 126. United States of America; 127. Tajikistan; 128. Greece; 129. Turkey; 130. Portugal; 131. Armenia; 132. North Korea; 133. Spain; 134. Turkmenistan; 135. Azerbaijan; 136. Albania; 137. Kyrgyzstan; 138. Uzbekistan; 139. Macedonia; 140. Georgia; 141. Italy; 142. Bulgaria; 143. Serbia and Montenegro; 144. Bosnia Herzegovena; 145. Croatia; 146. France; 147. Romania; 148. Switzerland; 149. Slovenia; 150. Moldava; 151. Hungary; 152. Austria; 153. Mongolia; 154. Kazakhstan; 155. Slovakia; 156. Ukraine; 157. Czech Republic; 158. Luxembourg; 159. Belgium; 160. Germany; 161. Poland; 162. Netherlands; 163. Ireland; 164. United Kingdom; 165. Belarus; 166. Denmark; 167. Lithuania; 168. Latvia; 169. Estonia; 170. Canada; 171. Russian Federation; 172. Norway; 173. Sweden; 174. Finland; 175. Iceland

Figure 2. Annual age-standardized incidence rates of cancer of the brain per 100,000 population, females, 175 countries. Source: Data from GLOBOCAN (1). Country label numbers are the same as in Figure 1.

Figure 3. Dose-response relationship between modeled serum 25(OH)D and incidence rates of brain cancer per 100,000 population in 175 countries. 2002. Source: Data from GLOBOCAN (1). Three outliers are label


$R^2 = 0.45$
$p \leq 0.0001$
Incidence rate per 100,000
Latitude
11
10
9
8
7
6
5
4
3
2
1
0
-1
-50
-40
-30
-20
-10
0
10
20
30
40
50
60
New Zealand
Australia
Brazil
Yemen
Colombia
Peru
Belize
Uruguay
Argentina
Paraguay
Chile
South Africa
Swaziland
Namibia
Equatorial Guinea
Bangladesh
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Mongolia
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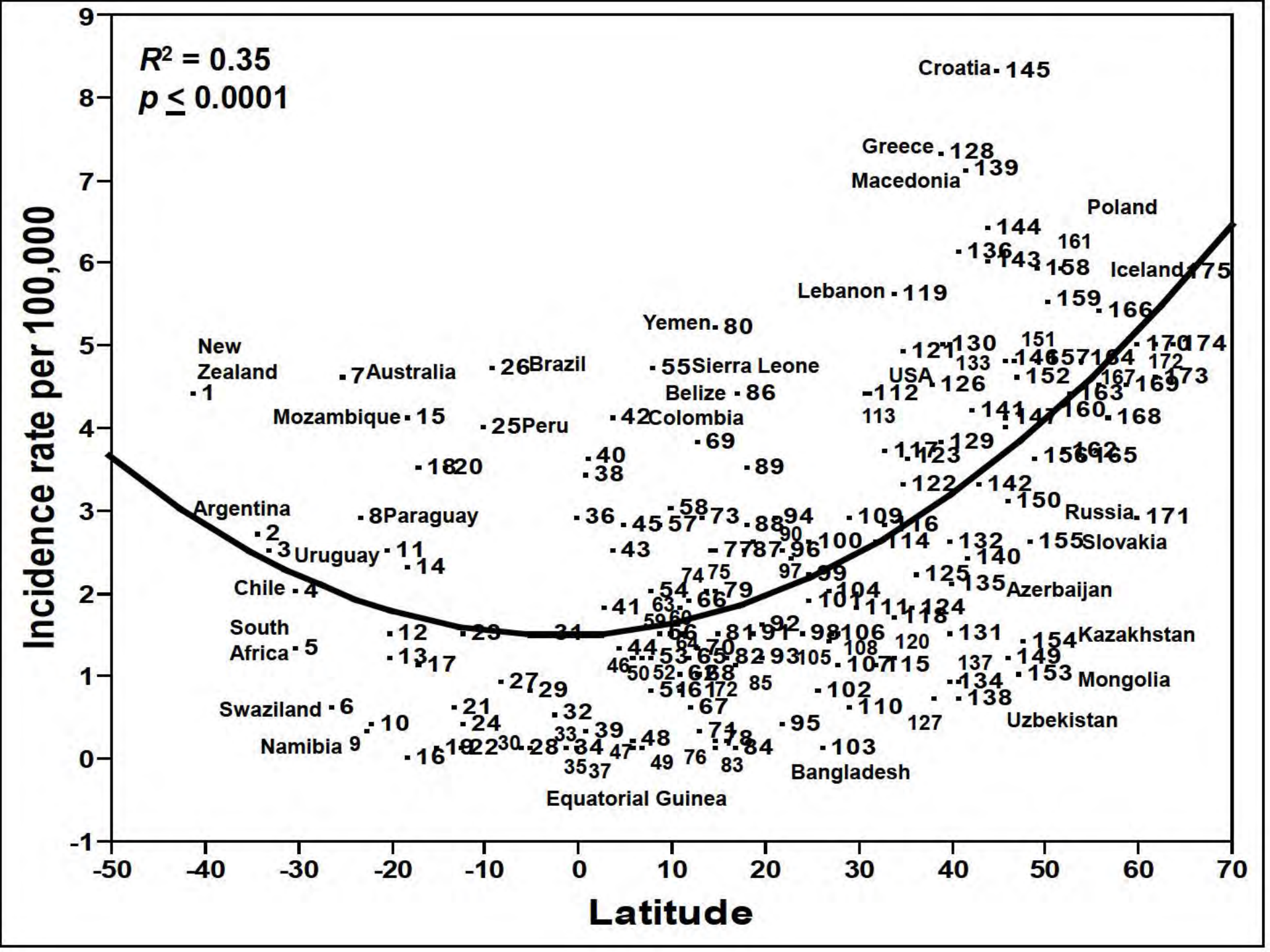
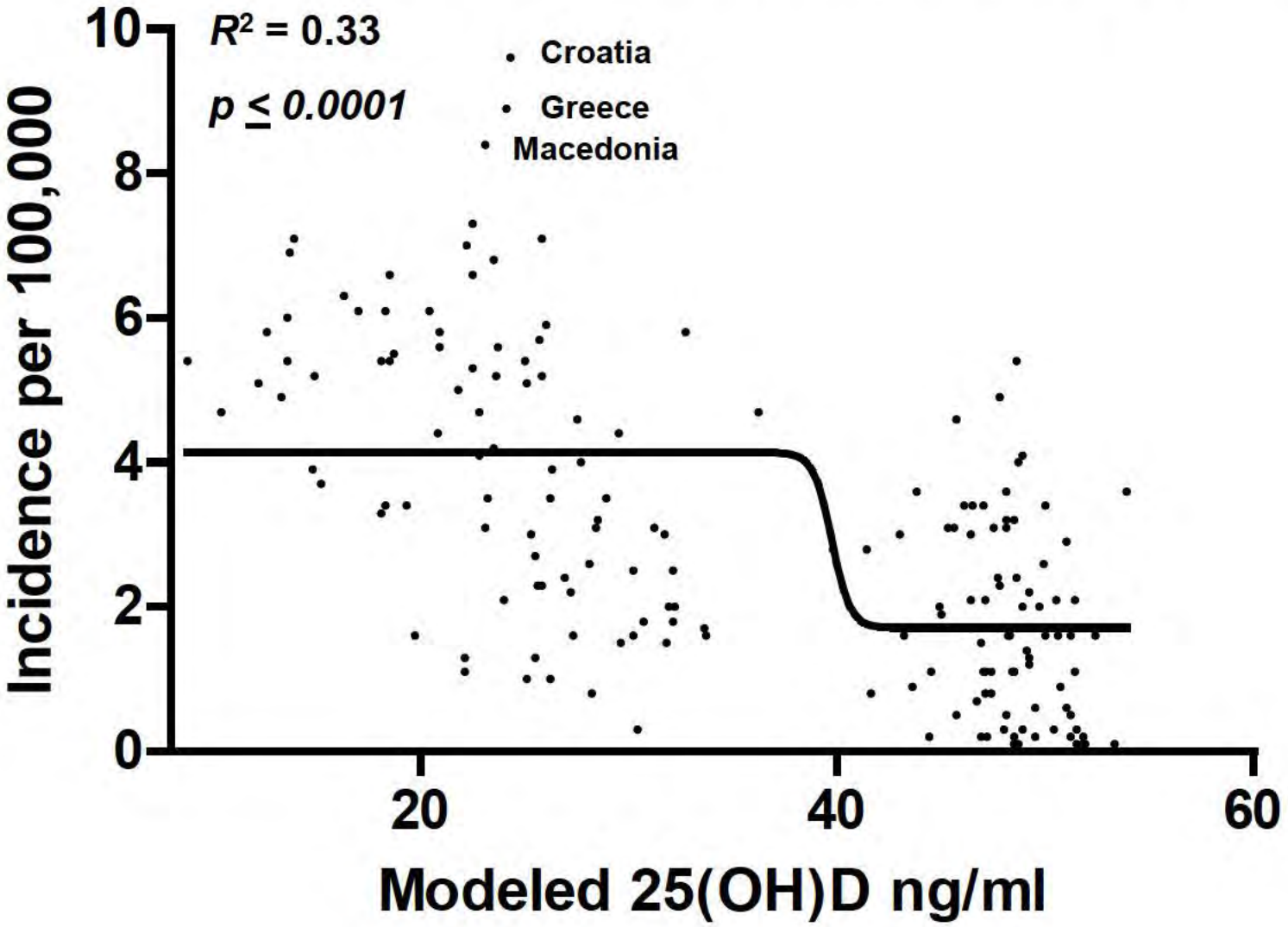
Belarus
Russia
USA
Israel
Lebanon
Macedonia
Greece
Croatia
Norway


$R^2 = 0.35$
$p \leq 0.0001$
Incidence rate per 100,000
Latitude
Croatia
Greece
Macedonia
Poland
Iceland
Lebanon
Yemen
New Zealand
Australia
Brazil
Sierra Leone
USA
Belize
Mozambique
Peru
Colombia
Argentina
Paraguay
Russia
Uruguay
Slovakia
Chile
Azerbaijan
South Africa
Kazakhstan
Mongolia
Swaziland
Uzbekistan
Namibia
Bangladesh
Equatorial Guinea

Annual age-standardized incidence rates of brain cancer, per 100,000 population, according to measured or modeled serum 25(OH)D, 2002



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14. ABSTRACT (maximum 200 words)

The purpose of this study was to determine whether an inverse association exists between latitude, solar ultraviolet B (UVB) irradiance, modeled 25-hydroxyvitamin D [25(OH)D] levels, and incidence rates of cancer of the brain. Incidence rates of brain cancer were higher at higher latitudes (R^2 for males = 0.45, $p<0.0001$: females $R^2 = 0.35$, $p<0.0001$). After adjustment for potential confounders, UVB irradiance ($p<0.0001$) and modeled serum 25 (OH)D were inversely associated with incidence rates.

Countries with low solar UVB irradiance and estimated mean serum 25(OH)D levels generally had higher age-standardized incidence rates of brain cancer. Since this was an ecological study, further research would be worthwhile of the association of prediagnostic serum 25(OH)D with incidence rate in studies of cohorts of individuals.

14. SUBJECT TERMS
Brain neoplasms, vitamin D, ultraviolet rays, incidence, alcohol, cigarettes, multiple regression, international comparisons.

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